REMARKS/ARGUMENTS

Claims 1-3 and 5-13 remain pending in this application. Claim 4 has been canceled. Claims 14-43 have been withdrawn without prejudice as the result of an earlier restriction requirement.

In view of the Examiner's earlier restriction requirement, Applicant retains the right to present claims 14-43 in a divisional application.

Claim Objections

Claim 4 was objected to by the Examiner for "being drawn to non-elected inventions such as ET-1, ET-2, ER-3, BQ3020, sarafotoxin 56c, and [$Ala^{1, 3, 11, 15}$] ET-1." Claim 4 has been canceled in view of this objection. Therefore, Applicant respectfully requests that this claim objection be withdrawn.

Claim Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 4-5 have been rejected under 35 U.S.C. §112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. More specifically, the Examiner states, "[c]laims 4-5 are rejected as vague and indefinite for reciting the term IRL1620 in association with being an endothelin B agonist as the sole means of identifying the claimed molecule." The Examiner goes on to state, "[t]he rejection can be obviated by amending the claims to specifically and uniquely identify IRL1620, for example, by chemical name and/or [*sic*] structure of IRL1620." Applicant has canceled claim 4 in view of the above-noted claim objection and has amended claim 5 to read, "[t]he method of claim [4] 1 wherein the endothelin B agonist comprises [IRL1620] Suc-[Glu^9, $Ala^{11,15}$]-Endothelin-1 (8-21). The term "Suc-[Glu^9, $Ala^{11,15}$]-Endothelin-1 (8-21)" is synonymous with IRL1620. Accordingly, claim 5 is now believed to be definite and Applicant respectfully requests that the rejection be withdrawn.

Claim Rejections Under 35 U.S.C. §102(b)

Claims 1-5 and 13 have been rejected under 35 U.S.C. §102(b) as being anticipated by Patterson *et al.* (IDS, WO 01/00198). Claim 1 of the present application claims, "[a] method of treating a solid tumor comprising administering to a mammal in need thereof a therapeutically effective amount of an endothelin B agonist and a therapeutically effective amount of a chemotherapeutic agent. The prior art of record does not disclose or suggest the above-noted features of claim 1. More specifically, the Patterson *et al.* reference does not disclose at least a therapeutically effective amount of an endothelin B *agonist*. Rather, per the Examiner's own admission, the Patterson *et al.* reference discloses IRL1620 as an inhibitor of endothelium activity (i.e., an antagonist) and not the presently claimed endothelin B agonist. The Patterson *et al.* discloses a method of treating cancer that "comprises administering to an individual in need of treatment for caner, an inhibitor of an endothelin receptor activity, in a therapeutically effective amount." The present application discloses a method of treating cancer using a therapeutically effective amount of an endothelin B *agonist*, which selectively increases blood supply to the tumor. This increases the delivery and efficacy of the accompanying chemotherapeutic agent. Therefore, endothelin B agonist can selectively increase the delivery of chemotherapeutic agents. To anticipate a claim, the reference must teach every element of the claim. M.P.E.P. §2131. The Patterson *et al.* reference does not teach at least a therapeutically effective amount of an endothelin B agonist. Accordingly, Applicant respectfully requests that this rejection be withdrawn and believes claim 1 is in condition for allowance.

Claims 2-3, 5 and 13 depend from claim 1, and because claim 1 defines novel and non-obvious patentable subject matter, claims 2-3, 5 and 13 define patentable subject matter. Furthermore, the prior art of record does not disclose or suggest the novel and non-obvious features of claims 2-3, 5 and 13. Accordingly, claims 2-3, 5 and 13 are in condition for allowance.

Claim Rejections Under 35 U.S.C. §103

Claims 1-6 and 13

Claims 1-6 and 13 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Patterson *et al.* (IDS, WO 01/00198, 2001) in combination with Rowinsky *et al.* (N. Engl. J. Med. 1995; 332: 1004-1014). In order to establish a prima facie case of obviousness, three basic criteria must be met, according to the Manual of Patent Examining Procedure, §706.02(j). These three criteria are repeated as follows. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference(s) or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference (or references) must teach or suggest all the claim limitations. Applicant submits that the Examiner has not established a prima facie case of obviousness for rejecting claims 1-6 and 13.

In regard to the first criterion of obviousness, there is no suggestion or motivation either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine reference teachings. The Examiner states, "Rowinsky *et al.* discloses paclitaxel...." The Examiner also states, "Patterson *et al* [*sic*] teaches....a method of treating a solid tumor comprising administering to a human in need thereof a therapeutically effective amount of IRL1620 and a therapeutically effective amount of a chemotherapeutic agent." Rather, more specifically, the Patterson *et al.* reference discloses administering "an *inhibitor of an endothelin receptor activity*, in a therapeutically effective amount" (emphasis added) and not a therapeutically effective amount of an endothelin B agonist as required by claim 1 of the present application. As a result, the Patterson *et al.* reference actually *teaches away from* applicant's present invention. As described above, the present application discloses a method of treating cancer using a therapeutically effective amount of an endothelin B agonist, which selectively increases blood supply to the tumor. This increases the delivery and efficacy of the accompanying chemotherapeutic agent. Therefore, an endothelin B agonist can selectively increase the delivery of chemotherapeutic agents. Moreover, per the

Examiner's admission, "Patterson *et al.* does not teach that the chemotherapeutic agent is paclitaxel. Accordingly, there is no suggestion or motivation either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the reference teachings.

In regard to the second criterion of obviousness, there is no reasonable expectation that the combination would be successful. For the above-noted reasons, if one were to combine the Patterson *et al.* reference with the Rowinsky *et al.* reference, not only would one not make obvious applicant's present invention for the reasons discussed above, but there is no reasonable expectation that the combination would be successful.

In regard to the third criterion of obviousness, the prior art references do not teach or suggest all the claim limitations. According to the Examiner's own admission, the Patterson *et al.* reference discloses IRL1620 as an inhibitor of endothelium activity (i.e., an antagonist) and not an "endothelium agonist" as required by claim 1 of the present application. The Patterson *et al.* reference discloses a method of treating cancer that "comprises administering to an individual in need of treatment for caner, an inhibitor of an endothelin receptor activity, in a therapeutically effective amount" as an antagonist anti-proliferative agent. The present application discloses a method of treating cancer using a therapeutically effective amount of an endothelin B agonist, which selectively increases blood supply to the tumor. This agonist increases the delivery and efficacy of the accompanying chemotherapeutic agent. Therefore, endothelin B agonist can selectively increase the delivery of chemotherapeutic agents. Accordingly, because at least this one claim element is not suggested or taught by the prior art of record, claim1 is in condition for allowance.

Claims 2-3, 5-6 and 13 depend from claim 1, and since claim 1 defines obvious patentable subject matter, claims 2-3, 5-6 and 13 define patentable subject matter. Furthermore, the prior art of record does not disclose or suggest the novel and non-obvious features of claims 2-3, 5-6 and 13. Accordingly, claims 2-3, 5-6 and 13 are in condition for allowance.

Claims 1-5 and 7-13

Claims 1-5 and 7-13 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Patterson *et al.* (IDS, WO 01/00198, 2001). Applicant submits that the Examiner has not established a prima facie case of obviousness for rejecting claims 1-5 and 7-13. (See the above-noted three basic criteria required by the M.P.E.P. for establishing a prima facie case of obviousness).

In regard to the third criterion of obviousness, the prior art reference does not teach or suggest all the claim limitations. According to the Examiner's own admission, the Patterson *et al.* reference discloses IRL1620 as an inhibitor of endothelium activity (i.e., an antagonist) and not an "endothelium agonist" as required by claim 1 of the present application. The Patterson *et al.* reference discloses a method of treating cancer that "comprises administering to an individual in need of treatment for cancer, an inhibitor of an endothelin receptor activity, in a therapeutically effective amount" as an antagonist anti-proliferative agent. The present application discloses a method of treating cancer using a therapeutically effective amount of an endothelin B agonist, which selectively increases blood supply to the tumor. This increases the delivery and efficacy of the accompanying chemotherapeutic agent. Therefore, endothelin B agonist can selectively increase the delivery of chemotherapeutic agents. Accordingly, because at least this one claim element is not suggested or taught by the prior art of record, claim 1 is in condition for allowance.

Claims 2-3, 5 and 7-13 depend from claim 1, and since claim 1 defines unobvious patentable subject matter, claims 2-3, 5 and 7-13 define patentable subject matter. Furthermore, the prior art of record does not disclose or suggest the novel and non-obvious features of claims 2-3, 5 and 7-13. Accordingly, claims 2-3, 5 and 7-13 are in condition for allowance.

All pending claims 1-3 and 5-13 are believed to be in condition for allowance and Applicant respectfully requests that a timely Notice of Allowance be issued in this case. In the event that the Examiner would like to discuss any portion of this response, or any other matter, a telephone call to the undersigned attorney is respectfully requested.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 50-3207.

Respectfully submitted,

Dated: 9/15/05

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